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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/643,450 | 08/19/2003 | Bernhard Hermann Heinrich Breier | ERNZ-01018US1 | 4401 |

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| EXAMINER | |
|---|---|
| KOSAR, ANDREW D | |
| **ART UNIT** | **PAPER NUMBER** |
| 1654 | |

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/643,450 | BREIER ET AL. | |
| | Examiner | Art Unit | |
| | Andrew D. Kosar | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *10 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *4,8,12-18,21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,9-11,19,20 and 23-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election of Group I (linking claims 1, 2, 5-7 and 9-11 and claims 3, and 21-26) and the species (1-3)IGF (GPE) in the reply filed on November 10, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

**Claims 4, 8, 12-18, 21 and 22** are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 11, 2005. Claims 1-3, 5-7, 9-11, 19, 20 and 23-26 have been examined on the merits. Please note, in the interest of compact prosecution, claim 2 has been included in the rejections and has been examined on the merits, in addition to the elected species.

### *Priority*

Applicant's claim for the benefit of a prior-filed application under 35 USC § 119(e) and/or under 35 USC §§ 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §§ 119(e) and 120 as follows:

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in New Zealand on August 19, 2002. It is noted, however, that applicant has not filed a certified copy of the NZ 520,866 application as required by 35 U.S.C. 119(b).

Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(a)-(d) based upon an application filed in New Zealand on December 11, 2000. It is noted, however, that applicant has not filed a certified copy of the NZ 508,779 application as required by 35

U.S.C. 119(b). Further, A claim for priority under 35 U.S.C. 119(a)-(d) cannot be based on said application, since the United States application was filed more than twelve months thereafter.

Acknowledgment is made of applicant's claim for priority based on an application 10/450,232. Because 10/450,232 was filed after the instant filing, the claim for the benefit of an earlier priority date cannot be made. Application 10/450,232 has a US filing date of October 24, 2003, while the instant Application has a filing date of August 19, 2003.

***Specification***

The disclosure is objected to because of the following informalities:

The claim of the benefit of priority to Application 10/450,232, and the lineage therein, is improper, as Application 10/450,232 is not a prior filed Application.

The use of the trademark(s), e.g., Long™R3IGF-1, has/have been noted in this application. A trademark should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant should capitalize each letter of the word or include a proper trademark symbol, such as ™ or ® following the word. Further, language such as "the product X (a descriptive name) commonly known as Y (trademark)" is impermissible, since such language does not bring out the fact that the latter is a trademark. Language such as "the product X (a descriptive name) sold under the trademark Y" is permissible. See MPEP § 608.01 (v).

Appropriate correction is required.

### *Claim Objections*

**Claim 1** is objected to because of the following informalities: While it is clear that the method results in a reduction in angiotensin II receptors in the kidneys of a mammal, the recitation in the preamble is inconsistent with this result, as it also embraces increasing angiotensin II receptors, with 'modulating'. Applicant is suggested to amend the claim to recite the method is for reducing the density and/or distribution of angiotensin II receptors.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 24-26** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 recites, "LR3IGF-1" and "Long™R3IGF-1", and it is unclear from the claims and specification as to what are "LR3IGF-1" and "Long™R3IGF-1". Further, Long is a trademark, and thus it is unclear as to what peptide, or formulation, is being claimed as "Long™R3IGF-1". It is noted that MPEP § 608.01 (v) states, "A trademark should be capitalized wherever it appears and be accompanied by the generic terminology."

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant should capitalize each letter of the word or include a proper trademark symbol, such as ™ or ® following the word. Further, language such as "the product X (a descriptive

name) commonly known as Y (trademark)" is impermissible, since such language does not bring out the fact that the latter is a trademark. Language such as "the product X (a descriptive name) sold under the trademark Y" is permissible. *See MPEP § 608.01 (v).*

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

**Claims 1-3, 5-7, 9-11, 23, 25 and 26** are rejected under 35 U.S.C. 102(b) as being anticipated by VICKERS (NZ 508,779, published January 26, 2001).

The instant claims are drawn to the method of modulating the density and/or distribution of angiotensin II receptors in a mammal via administration of an IGF-1 compound.

Vickers teaches administration of rhIGF-1 at 3 μg/g/day via subcutaneous implant to a rat (e.g. page 14).

Vickers teaches that dosages of IGF-I for subcutaneous injection are 40-80 μg/kg/day, 1 or 2x daily, and that the "active agent can be administered using any suitable route" including "orally or parenterally ,in combination with one or more suitable carriers or excipients" or as part of an implant (page 12). Vickers also teaches analogs of IGF-I (page 11).

Vickers teaches that "it is envisaged that the principle application of the method of the present invention will be to humans, either as adults or juveniles, although the method may also have application to non-human mammals" (page 10). "Subjects may be selected for treatment on the basis of a review of maternal history during pregnancy." (page 10).

Vickers teaches that, "IGF-I therapy may also ameliorate obesity, hyperphagia and hypertension by differential regulation of downstream signaling networks via the IRS, RAS and IGF-I receptor signaling pathways by independent and complementary mechanisms." (page 28).

Vickers further teaches that, "Of particular clinical benefit is the potential use of IGF-I, analogues or ligands, in individuals who have been exposed to fetal programming but are otherwise essentially healthy" (page 28).

Because Vickers teaches the same dose of the same compound, and genus of compounds instantly claimed, is administered in the methods therein, it is inherent that in practicing the methods of Vickers, one would be practicing the instantly claimed method, as the compound when administered at the dose in Vickers would inherently modulate the density and/or distribution of angiotensin II receptors, as a compound and its properties cannot be separated.

**Claims 1-3, 6, 7, 9, 11 and 23** are rejected under 35 U.S.C. 102(b) as being anticipated by IKENASIO (M.H. Vickers, et al. Endocrinology (2001) 142(9), pages 3964-3973). For clarity in distinguishing between this reference and Vickers, *supra*, the secondary author is cited here.

Ikenasio teaches that, "Furthermore, recent evidence suggests that IGF-I can interact with the renin-angiotensin system (RAS) and may alter angiotensin II expression via angiotensin type 1 receptor regulation." (page 3965).

Ikenasio teaches administration of rhIGF-1 at 3 μg/g/day via subcutaneous implant to a rat (*IGF-I infusion*, page 3965). The rats were bred as the model for syndrome X/fetal programming (e.g. last paragraph page 3972).

Ikenasio teaches that, "The highly significant increase in kidney weight with IGF-I treatment may also be an important factor in reduction of SBP via changes in renal plasma flow

and glomerular filtration rate. Given recent *in vitro* observations, it is tempting to speculate that IGF-I treatment may also reduce blood pressure by down-regulating the local RAS and limiting angiotensin II formation through mediation of the angiotensin type 1 receptor (page 3972).

In practicing the method of Ikenasio, one is inherently practicing the instantly claimed method.

**Claims 1-3, 5-7, 9-11, 19, 20, 23, 25 and 26** are rejected under 35 U.S.C. 102(b) as being anticipated by CLARK (US Patent 5,565,428).

The instant claims are presented *supra*. The claims are further drawn to administration of an ACE inhibitor in combination with the IGF-I compound.

Clark teaches that , "In addition, [ACE] inhibitors may be beneficial in conjunction with the IF-I treatment of renal disorders." (column 11, lines 37-39), and that "In the treatment of [CHF], ACE inhibitors may be useful together with IGF-I by reducing systemic vascular resistance and relieving circulatory conjestion." (column 11, lines 40-43).

Clark teaches that the ACE inhibitors that can be used include quinapril, ramipril, captopril, benazepril, folinopril, lisinopril and enalapril. (column 11, lines 44-50).

Clark teaches that "Renal function can be enhanced by administration of IGF-I at 100 μg/kg subcutaneously each day"(column 12, lines 54-55).

Because Clark teaches the combination and that the IGF-I is administered within the instantly claimed dose range that is claimed, the administration inherently would modulate the density and/or distribution of angiotensin II receptors as instantly claimed.

**Claims 1-3, 5-7, 9-11, 23, 25 and 26** are rejected under 35 U.S.C. 102(b) as being anticipated by GLUCKMAN (US Patent 5,922,673).

The instant claims are presented *supra.*

Gluckman teaches a method for treating a pregnant mammal (including a human) via administration of IGF-I or an analog. In humans, the dose is administered at 40-200 μg/kg/day (column 2, lines 1-5).

Gluckman teaches that IGF-I can be administered alone or in combination with another antihypertensive treatments (column 2, lines 15-17).

Gluckman teaches that the IGF-I can be administered by implant, subcutaneous, intramuscular, intranasal or oral routes of administration (column 2, lines 6-14).

Gluckman teaches treating hypertension in a pregnant mammal with IGF-I or an analogue of IGF-I (claim 1), with IGF (claim 5) and IGF at doses of 40-2000 μg/kg and 40-200 μg/kg (claims 10 and 11) and in combination with an other antihypertensive (claim 13).

Because the same compound is being administered and at the same doses as instantly claimed, in practicing the method of Gluckman, one would inherently be practicing the instantly claimed method.

**Claims 1, 3, 6, 7, 9-11, 23 and 24** are rejected under 35 U.S.C. 102(b) as being anticipated by WILLIAMS (WO 95/17204 A1, for clarity in distinguishing between this reference and Gluckman, *supra*, the secondary author is cited here).

Williams teaches administration of GPE to mammals (e.g. claim 2), as a pharmaceutical (claim 10), orally, IV, subcutaneously, IP, IM, or inhalation (claim 16) and at a dose of 1 μg to about 100 mg/kg/day (claim 20). In looking to the specification, it is noted that the doses

administered to the test subjects were 2 to 200 μg (Example 5, page 19), and in other instances 'preferably' 1 mg/kg (Example 2, page 18).

Because the same compound is being administered and at doses of an overlapping range, with doses described in the specification within the instantly claimed range, in practicing the method of Williams, one would inherently be practicing the instantly claimed method.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 1-3, 5-7, 9-11, 19, 20 and 23-26** are rejected under 35 U.S.C. 103(a) as being unpatentable over GLUCKMAN, as applied to claims 1-3, 5-7, 9-11, 19, 20, 23, 25 and 26, *supra*, in view of CLARK, as applied to claims 1-3, 5-7, 9-11, 19, 20, 23, 25 and 26, *supra*, Ikenasio, as applied to claims 1-3, 6, 7, 9, 11 and 23, *supra*, Vickers, as applied to claims 1-3, 5-7, 9-11, 23, 25 and 26, *supra*, WILLIAMS, as applied to claims 1, 3, 6, 7, 9-11, 23 and 24, *supra*, DIMARCHI (US Patent 5,622,932), and AMBLER (US Patent 5,420,111, for clarity in distinguishing between this reference and Gluckman, *supra*, the secondary author is cited here).

The instant claims are presented *supra*.

The teachings of Gluckman, Clark, Ikenasio, Williams and Vickers are presented *supra*.

Ambler teaches, "Although the studies to be discussed herein concentrate on the use of IGF-1, the claims extend to IGF-2 and analogues of IGF-1 and IGF-2 as these are known to exert a similar biological effect to IGF-1 (Schoenle et al., Acta Endoc. 108: 167-174, 1985)." And "By "analogues" of IGF-1 and IGF-2 is meant compounds having the same therapeutic effect as IGF-1 or IGF-2 in humans and animals. These can be naturally occurring analogues of IGF-1 or IGF-2 (eg truncated IGF-1 or DES 1-3 IGF-1 synthesized by GENENTECH, INC. and KABI PHARMACIA) or any of the known synthetic analogues of IGF-1 and IGF-2." (column 3, lines 47-58).

Williams further teaches the tripeptide GPE is a truncated form of IGF, synthesized or produced after proteolytic cleavage of IGF-1, and that GPE functions like IGF-1 (throughout). Thus, because it functions like IGF-1, it is considered an analog, as defined by Ambler.

DiMarchi teaches IGF-1 analogs, and production of IGF-1, or analogs, through recombinant means (e.g. column 9, line 44+) and recombinant synthesis of human IGF-1 (e.g. citing Ueda, US Patent 5,019,500, column 8, lines 1-3).

DiMarchi teaches treating an individual afflicted with a condition selected from diabetes, diabetic neuropathy, insulin-resistance, IGF-resistance, and other conditions, via administration of an IGF-1 analog (claim 8).

DiMarchi teaches that the dose administered is between 1 and 1000 μg/kg (column 12, line 13+).

The difference between the instant claims and that which is taught by the references, is that while the art teaches administration of IGF-I analogs, the art does not teach the specifically recited IGF-I compounds of claim 24, except GPE.

It would have been obvious to one of ordinary skill in the art to have administered any analog of IGF-1 or IGF-2, alone or in combination with an ACE inhibitor, with the expectation of having a similar outcome from compounds that are considered to be analogs, as defined by Ambler.

One would have been motivated to have practiced the method with any IGF-1 or IGF-2 analog as the methods of Gluckman and DiMarchi can be practiced with any IGF-1 or analog, and because IGF-I analogs are well known in the art to be compounds that act like IGF.

One would have had a reasonable expectation for success in practicing the methods of Gluckman and DiMarchi with any analog, as analogs of IGF-I and IGF-2 are known in the art to have a similar effect to IGF-1 and IGF-2.

With regards to the composition which is administered (IGF-1 and an ACE inhibitor): As set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980), "It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; the idea of combining them flows logically from their having been individually taught in prior art."

In the instant case, IGF-1 and ACE inhibitors are known to be co-administered to treat renal disorders, and thus it would have been obvious to make and use a combination therapy of an IGF and ACE inhibitor.

With regards to administration: It would have been obvious to administer a composition of IGF-1, or an analog, and any ACE inhibitor, including captopril, for the at least additive effect achieved by their co-administration. One would have been motivated to administer both IGF-1 and an ACE inhibitor for the benefit of increased efficacy in treating a, with a reasonable

expectation for success in treating a renal disorder, and thus, in treating a renal disorder, one would intrinsically be modulating the density and/or distribution of angiotensin II receptors.

With regards to the doses administered, the references cited above teach administration of IGF-1 or an IGF-1 analog at various doses. It would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g. dose administered), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2145.05).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Conclusion***

**NO CLAIMS ARE ALLOWED.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 8am-430pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571)272-0974. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Andrew D. Kosar, Ph.D.
Art Unit 1654

1/23/07
ANISH GUPTA
PRIMARY EXAMINER